Session 2: Global Perspectives of Malaria

Changing pattern of antimalarial drug resistance

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Keywords: malaria; antimalarials; resistance

Summary

With the current increase of international travel and increasing drug resistance, United Kingdom residents stand a high risk of contracting malaria when they visit endemic countries. The development of antimalarial agents from old traditional plant remedies to modern synthetic drugs is briefly reviewed. Resistance to the latter has spread rapidly since the 1950s, culminating in the widespread distribution of multiple drug-resistant strains of *Plasmodium falciparum* in most endemic areas. There is a danger that such parasites may rapidly develop resistance even to new compounds such as mefloquine, halofantrine or artemisinin unless the use of such compounds is carefully controlled. The few developments, including new drugs and ways of reversing existing resistance, are also briefly reviewed in this paper. Emphasis is laid on the need to revert to classical methods of protection against malaria vectors since it is unlikely that a protective vaccine will become available in the near future.

Introduction

The population of the United Kingdom is today at greater risk of contracting malaria than at any time since World War I, due to the popularity of international travel[1] and an exponential increase in parasite resistance to antimalarial drugs. As a consequence of the second of these factors, an entire symposium was devoted to quinine and other *Cinchona* derivatives in the prophylaxis and treatment of malaria in 1987[2]! This event might have encapsulated the entire history of antimalarial drugs but for one fact - quinine is *not* the oldest antimalarial drug. That honour goes to another traditional medicinal plant, *Artemisia annua* (Qinghao), which was recorded in China as a febrifuge more than 2000 years ago[3].

Outside China, however, only quinine was familiar and it was widely used for the prevention and treatment of the intermittent fevers that subsequently came to be known as malaria. Quinine was the only effective drug known in Europe and its limitations became very evident during World War I when thousands of troops contracted falciparum and vivax malaria in various theatres of war. Many died or continued to suffer from chronic relapses for many years after the war.

Synthetic antimalarials - the first half century

The advent of the golden age of experimental chemotherapy and the search for Ehrlich's 'Magic bullets' produced a flurry of research in medicinal chemistry, especially in Germany, and from these endeavours a new generation of synthetic antimalarial drugs emerged. The first of these, a 6-methoxy-8-aminoquinoline, later known as pamaquine, which was described in 1926, was found to prevent the relapses that characterize infection with *Plasmodium vivax* (the nature of the liver stages responsible for these relapses was not discovered until 1980). In 1932 a 9-aminoacridine, known first as atebrin and subsequently as mepacrine, was shown by German investigators to have a potent action against the asexual, intraerythrocytic stages that are responsible for the acute malaria attack. During World War II quinine came to be largely replaced by pamaquine and mepacrine and these drugs remained the most widely used antimalarials until the early 1950s.

By then several new compounds were emerging from the large antimalarial screening programme that had been set up in the UK and the USA. Chloroquine, first synthesized in the pre-war German research programme and subsequently 'rescued' from the German army by allied troops, proved to be as effective as mepacrine and far less toxic. Its arrival on the scene shortly after the emergence of DDT as a residual insecticide permitted the evolution of the ambitious plan for the global eradication of malaria that was launched with great enthusiasm by the World Health Organization (WHO) in the mid-1950s[4]. A safer analogue of pamaquine, primaquine, appeared at about the same time and this was rapidly adopted to eliminate relapses of *P. vivax*, the next most common parasite to *P. falciparum* and the dominant species in the Indian sub-continent.

Two compounds, of entirely different chemical classes, which have, as was shown later, a common mode of action, were synthesized in the UK. The first of these, on which much effort had been devoted during World War II, was a biguanide, proguanil. This was soon followed by pyrimethamine, a 2-4-diaminopyrimidine. Both proved to be potent inhibitors of the dihydrofolate reductase of malaria parasites, the former through its active triazine metabolite, cycloguanil, the structure of which is very similar to that of pyrimethamine. These 'antifols' were soon found to be very effective as prophylactic agents but too slow to gain a place in therapy.

Emergence of drug resistance

Although it was suspected that malaria parasites could become resistant to quinine and pamaquine, the few experiments that were carried out, mainly using simian or avian malaria models, prior to World War II indicated that resistance was unlikely to prove a major problem in practice[5]. However, the advent of the 'antifols' which had been derived partly from the demonstrated

antimalarial properties of the original sulphonamides, reopened the question. It was soon shown not only that the non-human parasites used for experimental studies could readily become resistant to proguanil or pyrimethamine, but so too could *P. falciparum, P. vivax* and *P. malariae* in man, both under experimental and natural conditions. However, early experiments with the animal and avian models led to the belief that malaria parasites did not have the ability to develop a significant level of resistance, to either mepacrine or to chloroquine. This gave rise to a false sense of security and the belief that, even were the human parasites to become resistant to the 'antifols', they would remain responsive to chloroquine.

Events in the late 1950s, particularly the wholesale use of chloroquine and pyrimethamine for mass chemotherapy as a major tool in the global eradication campaign and, subsequently, the onset of the war in Indochina (which involved the exposure of thousands of non-immune troops to intense malaria transmission) soon shattered this belief. Several foci of chloroquine-resistant *P. falciparum* were identified in the early 1960s, in Panama, Colombia and Venezuela in South America with others in Thailand, Cambodia (Kampuchea) and Vietnam. The first of these reports were met with some scepticism but they were rapidly followed by others, which indicated that this type of resistance was by no means rare. Moreover, it was shown that chloroquine resistance could readily be induced in a more relevant experimental model than had formerly been available, namely *P. berghei* (a parasite of African thicket rats) in the laboratory mouse[5]. As in the first human cases of *P. falciparum*, resistance to chloroquine in *P. berghei* was not automatically associated with resistance to the 'antifols', although cross-resistance was clearly present to other 4-aminoquinolines, such as amodiaquine, as well as to mepacrine.

In Vietnam it was soon found that chloroquine-resistant falciparum infections were fully responsive to quinine, the only problems then being, firstly, that quinine had sometimes to be given in sub-toxic dosage and, secondly, it became a very scarce commodity. To counter this dangerous situation the US Army launched a massive programme to seek new drugs and to date over 300 000 compounds have been screened! Little enthusiasm was shown in antimalarial research by the great majority of commercial organizations, in spite of efforts by the World Health Organization to encourage further antimalarial research. However, it was already known that combinations of pyrimethamine with some sulphonamides, eg sulphadiazine, would cure some chloroquine-resistant falciparum infections[6]. Investigators in Hoffman la-Roche reported that a combination of pyrimethamine with a new, long-acting sulphonamide, sulfadoxine, was even more effective and this combination, under the trade name Fansidar, came into extensive use, both for prophylaxis and for therapy, in areas where the problem of chloroquine resistance existed. Experience showed that Fansidar not only remained effective in practice but served to delay the spread of resistance to its pyrimethamine component for some 15 years; resistance to the latter, when used on its own, had become apparent on several continents in less than one year. More recently two factors have emerged that seriously limit the value of Fansidar. One is the now familiar risk of serious skin reactions to sulfadoxine and other long-acting sulfonamides. While the risk is relatively low, most authorities feel that it is sufficient to prohibit the continuing use of Fansidar for prophylaxis; as a result the drug is now largely restricted for single-dose therapy of falciparum attacks[7]. The second factor is the emergence in several geographical areas of multiple drug resistance in *P. falciparum*. This phenomenon spread rapidly from its original foci in Southeast Asia and South America but only appeared in about 1978 in Africa; from there it has now become disseminated from the East coast across the continent, taking in most of Central Africa and many of the countries of West Africa[5].

Until relatively recently even multiple drug-resistant strains of *P. falciparum* (and, so far, the problem in man is limited to that species) were responsive to quinine. Perhaps not surprisingly, therefore, the most effective compounds to emerge from the US Army antimalarial screen, mefloquine and halofantrine, proved to be related both chemically and in their modes of action to quinine. Mefloquine, a long-acting, blood schizontocidal amino-alcohol with a quinoline nucleus, which was developed (from the mid-1970s) under the auspices of the UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases (the TDR programme), in close collaboration with the US Army and the pharmaceutical industry, is now available commercially in a small number of countries. In principle these countries are limited to endemic areas, where multiple drug-resistant *P. falciparum* poses a major public health problem (the list is increasing almost daily), and non-endemic countries, where it will be available essentially for prophylaxis or therapy in travellers. Mefloquine will, for example, be launched in the UK during 1989. Halofantrine, which has a much shorter duration of action[8], has only recently been introduced and, so far, in a few countries only, as an alternative to mefloquine.

Experiments in animal models long ago demonstrated the ease with which resistance to quinine and to related compounds, such as mefloquine, can emerge under drug selection pressure when this is exerted on parasites that already possess a significant level of resistance to chloroquine. The relevance of this observation to human malaria was revealed when clinicians in Thailand reported that the response of some local strains of *P. falciparum* to quinine was progressively deteriorating[5] and this observation has now been extended to other parts of the world, including some countries in Latin America and in Africa where falciparum malaria used to be renowned for its high level of sensitivity to quinine. Even more disturbing are the increasing, if still isolated, reports of resistance to mefloquine. These are hardly to be wondered at when they arise from areas where chloroquine resistance is solidly established, such as the infamous Thai-Kampuchean border; however, it is particularly disturbing to hear of the existence of such parasites in other areas, for example, in East Africa[9], where the problem of multiple drug resistance is a relatively new phenomenon. Moreover, there is good reason to believe that such resistance will extend also to halofantrine which has hardly yet been used[10]. In the face of this increasing spectrum of resistance to antimalarials, what remains?

Future prospects

This is the point at which, in considering this subject, the pendulum takes a full swing - back to China. It is just a decade since Chinese investigators isolated the main ingredient of Qinghao that is responsible for its antimalarial action[3]. It proved to be a sesquiterpene lactone, now called artemisinin (Qinghaosu). This compound is a blood schizontocide with an inhibitory action on parasite protein and nucleic acid metabolism that is even more rapid than that of quinine. From the parent compound a number of analogues have now been derived that possess improved pharmacokinetic properties and potency. They include artemether, arteether, sodium artesunate and artelinic acid. The artemisinin family is active against strains of *P. falciparum* and of experimental species such as *P. berghei* that are multiple drug-resistant, and they appear to have a very low level of mammalian toxicity. Fortunately, their short duration of action renders them of limited value for prophylaxis since parasites readily become resistant to these compounds if the compounds are used alone[11]. It is possible, however, that the judicious use of appropriate combinations of sesquiterpene lactones with certain compounds of the aminoalcohol series, such as mefloquine (which have already been demonstrated to have a synergistic effect) may serve to impede the emergence of resistant mutants, at least for some time - just as did the synergistic combination of pyrimethamine with sulfadoxine. It is, however, very unlikely that a combination will ever be discovered, even of such powerful blood schizontocides, that completely prevents the emergence of multiple drug resistance in *P. falciparum*.

Light has recently been shed on the root of this problem by the discovery that resistance to chloroquine can be reversed by certain drugs that are known to act as calcium channel blockers or antagonists of calmodulin (eg verapamil, desipramine)[12], just as multiple drug-resistance can be reversed in some cancer cell lines. Recent work has demonstrated the presence of a type of 'multiple drug resistance protein' (MDR) in *P. falciparum* and a low level of amplification of the gene coding for this protein in some isolates that are resistant to chloroquine[13]. It is unsure yet, however, to what degree, if any, this mechanism is responsible for resistance to aminoalcohols and it is has been clearly demonstrated that resistance to 'antifols' is associated with mutations in the genes coding for the synthesis of parasite dihydrofolate reductase[14]. Few other antimalarials have appeared on the horizon in recent years. However, a naphthoquinone code named 566C80 is currently commencing Phase I clinical trials and new compounds may emerge that can, like desipramine, reverse chloroquine resistance but without producing undesirable side effects.

Conclusions

What choice does this leave us with at the present time for prophylaxis, or for the therapy of established malaria infections? First, it must be emphasized that the problem of multiple drug resistance is limited to *P. falciparum*. The likelihood of an effective antimalarial vaccine becoming available for prophylaxis in the near future, as had been over-optimistically forecast, is receding rapidly as increasing obstacles appear in vaccine development programmes[15]. Although 'antifol' resistance is common in the other species that affect man, chloroquine remains an effective drug, both for prophylaxis and treatment, in the management of these species. Primaquine produces a radical cure of infection due to *P. vivax or P. ovale* by its action on the hypnozoites that cause relapses of these infections, even though a relatively high dose must be used against certain strains of *P. vivax*, such as those that occur in the Southwest Pacific.

No currently available single drug or drug combination can be guaranteed to afford complete protection against *P. falciparum* although chloroquine in many West African countries remains effective at the time of writing. Other papers in this symposium will discuss this matter in further detail. What has become increasingly clear in the last few years is the necessity of pursuing 'old-fashioned' methods of prophylaxis - insect repellents, protection by mosquito nets (preferably impregnated with a modern insecticide, such as one of the synthetic pyrethroids), fumigant insect repellents, and appropriate dress after dusk. All of these practical measures serve a valuable function in limiting the number of potentially infective bites[16]. Adherence to the advice from *informed* sources, and the continuation of antimalarial prophylaxis for the prescribed period of four weeks' post-exposure all contribute to protection of the traveller; however, chemoprophylaxis for those resident for longer periods in endemic areas may be more difficult. Of paramount importance is the need to avoid the irrational deployment of any newly developed antimalarial, especially on its own. History has demonstrated only too clearly the ease with which *P. falciparum* can become resistant to *any* antimalarial to which it is exposed. The discovery and development of new drugs, especially drugs that will ultimately be used against parasitic diseases, demands an enormous investment in money and manpower. This investment is becoming increasingly difficult to obtain in today's highly competitive and commercially motivated world. It is, therefore, vital that we make the best possible use of any new drugs that may be developed in the years to come since it is certain that malaria will remain with us for the foreseeable future.

References

1 Phillips-Howard PA, Breeze E, Lakin C, Bradley DJ. Short term travel to malarious areas: malaria risk in British residents. *Travel Med Int* 1988;**6**:51-60

2 Van der Kaay HJ, Overbosch D, eds. Q-Now! Proceedings of the symposium on the use of quinine and quinidine in malaria. *Acta Leiden* 1987;**55**:1-221

3 Klayman DL. Qinghaosu (artemisinin): an antimalarial drug from China. *Science* 1985;**228**:1049-55

4 Bruce-Chwatt LJ. History of malaria from prehistory to eradication. In: Wernsdorfer WH, McGregor I, eds. *Malaria. Principles and practice of malariology*. Edinburgh: Churchill Livingstone, 1988:1-59

5 Peters W. *Chemotherapy and drug resistance in malaria*, 2nd edn, vols 1 and 2. London: Academic Press, 1987

6 Scholer HJ, Leimer R, Richle R. Sulphonamides and sulphones. In: Peters W, Richards WHG, eds. *Antimalarial drugs II Current antimalarials and new drug developments*. Berlin: Springer-Verlag, 1984:123-206

7 Anonymous. *International travel and health. Vaccination requirements and health advice. Situation as on 1 January 1989*. Geneva: World Health Organization, 1989

8 Broom C. Human pharmacokinetics of halofantrine hydrochloride. *Parasitol Today* 1989;**5**(suppl):15-20

9 Kilimali VAEB, Mkufya AR, Kilama WL. Low resistance of *Plasmodium falciparum* to mefloquine in Tanga region. *Trans R Soc Trop Med Hyg* 1989;**83**:162-4

10 Peters W, Robinson BL, Ellis DS. The chemotherapy of rodent malaria XLII. Halofantrine and halofantrine resistance. *Ann Trop Med Parasitol* 1987;**81**:639-46
11 Chawira AN, Warhurst DC, Peters W. Qinghaosu resistance in rodent malaria. *Trans R Soc Trop Med Hyg* 1986;**80**:477-80
12 Martin KS, Oduola AMJ, Milhous WK. Reversal of chloroquine resistance in *Plasmodium falciparum* by verapamil. *Science* 1987;**235**: 899-902
13 Foote SJ, Thompson JK, Cowman AF, Kemp DJ. Amplification of the multidrug-resistance gene in some chloroquine resistant isolates of *P. falciparum*. *Cell* 1989;**57**:921-30
14 Peterson DS, Walliker D, Wellems TE. Evidence that a point mutation in dihydrofolate-thymidylate synthase confers resistance to pyrimethamine in falciparum malaria. Proc Natl Acad Sci USA 1989;**85**: 9114-18
15 Miller LH, Good MF. The main obstacle to a malaria vaccine: the malaria parasite. *Vaccine* 1988; **6**:104-6
16 Peters W. How to prevent malaria. *Trop Doct* 1987; **17**:1-3

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